IN THE UNITED STATES PATENT OFFICE

Application Serial No. 07/675,908

Filed: July 3, 1991

Applicants: Dr. Rudolf Falk
Dr. Samuel S. Asculai
(Now assigned to
Hyal Pharmaceutical Corporation)

Title: THE USE OF HYALURONIC ACID OR ITS DERIVATIVES TO ENHANCE DELIVERY OF ANTINEOPLASTIC AGENTS

Inventors: Dr. Rudolf Falk,
Dr. Samuel S. Asculai

Examiner: Dr. Kathleen Fonda

Group Art Unit: 1806 Extended Due Date: September 5, 1996

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 Jefferson Davis Highway
Crystal Plaza 2, Room 1B03
Arlington, Virginia
U.S.A. 22202

DECLARATION OF JOSEPH ROBERT EMMOTT FRASER under § 1.132

I, JOSEPH ROBERT EMMOTT FRASER, M.D., make oath and say as follows:

1. I am the same Joseph Robert Emmott Fraser, M.D. who filed the Declaration dated September 5, 1996 in the prosecution of the above-identified application.

2. THE OFFICE ACTION

For the purposes of preparing this Declaration, I was asked to review the Official Action Summary issued by the Patent Office, identified as paper #33, and particularly the objections to the specification relating to the breadth of the claims which read on methods of treating:

(a) an arbitrary disorder or condition;

(b) cancers generally;

(c) side effects of drugs; and

(d) AIDS.

With regards to this ground of objection, the Examiner in the action states that there has been no disclosure adequate to enable the entire scope of these claims in the specification as filed. I note the statement in the action that "Significantly no declarant has stated that the instant invention would be expected to be broadly useful to treat any condition whatsoever". I will comment upon this statement in my declaration.

I have also been asked to comment about the dosage amount being indefinite having regard to the use of the expression "10mg/70kg person and 1000mg/70kg person".

I have also been asked to discuss the expression "dose excess" and the Examiner's statement that the expression "of dosage excess" having regard to what is normally understood by persons skilled in the art is not sufficient to the Examiner. According to the Examiner, this was not convincing because without knowing the intended result of administration of component (1), it would not be possible to determine when a dose excess had been reached.

Additionally, I was also made aware firstly of the rejection by the Examiner of the dosage claims for the composition based on Della Valle (U.S. Patent 4,736,024); and secondly, the rejection by the Examiner of the claims for both dosage and methods of treatment by the combination of prior art including Selfter (U.K. Patent 769287), Schultz (U.S. Patent 4,808,576), Della Valle (U.S. Patent 4,736,024), and Balazs (Polymers in Chemistry). I am advised by Ivor Hughes, Patent Agent, that this latter rejection was based on the asserted obviousness of the subject matter of the claims that would follow the reading of Selfter et al (U.K. Patent 769287) read in view of Schultz et al (U.S. Patent 4,808,576) and Della Valle et al (U.S. Patent 4,376,024 *sic* - I believe this was a typing slip and was meant to read U.S. Patent 4,736,024), as further evidenced by E.A. Balazs and P. Bland in the article "Polymers in Cosmetics. Hyaluronic Acid: Its Structure and Use", Cosmetics & Toiletries, 1984, Vol. 99, pps. 65-72.

I understand from page 7 of the action that, according to the Examiner, Della Valle's suggestion of dermatological preparations would provide ample motivation for one of ordinary skill in the art to alter the amount of hyaluronic acid present in the composition. The Examiner also notes that dermatological preparations which contain hyaluronic acid are commercially available in the United States, referring to Physicians' Desk Reference, page 1868R. The only relevant reference that I can find in the 50th Edition (1996) of the Physicians' Desk Reference is on page 1827, which describes DML Moisturizer and Skin Lubricant. This contains SPF 15 and a number of other potential moisturizers and lubricants; a copy is attached as Exhibit 1.

With respect to the method claims the Examiner states that the prior art relied upon by the Examiner does indeed suggest to do what Applicants have done. According to the Examiner it was not relevant that the Applicants may

have discovered a particular advantage to the suggested method which may not have been recognized by prior workers in the field.

3. REPRESENTATIVE CLAIMS

With this Official Action, I was also given a copy of what I was advised by Ivor M. Hughes are representative proposed claims, a copy of which I attach as Exhibit 2 to this my declaration. For the purposes of this declaration, I have been advised that the Applicants filed the first application for this invention in September 1989 in Canada and filed a PCT application which enlarged the disclosure of the original case which had effect in the United States as if filed in the United States on September 18, 1990 and which claims priority from the Canadian Application.

4. STATE OF THE ART

In this section I discuss the state of the art with respect to the use of forms of hyaluronan and what would have been known to persons skilled in the art at the time of filing of the Canadian Application in September 1989 and the PCT application filed in September 1990. The prime question that I shall address here is whether the claims made in this application (representative examples of which are attached as Exhibit 2 to this my declaration), were taught in the application, would have been obvious at that time to persons skilled in the art, or would have been obvious from a reading of the patents of Seifter, Della Valle and Schultz cited in Section 2 and of the medical and scientific literature of the time. Where appropriate to any additional comments now made, I shall refer to articles that particularly illustrate a point that I wish to make, to the references cited by the Examiner, or to my previous declaration.

For reasons given in my previous declaration, U.K. Patent 769,287 (Seifter and others) does not, in my opinion, relate to hyaluronic acid, which hyaluronic

acid is by definition a polymer. Seifter et al relates to oligosaccharides (oligomers) derived therefrom. It must be emphasized that Seifter's preparation was not intended for application to the surface of the skin but specifies injection. Seifter has not become generally known to persons skilled in the art. Although the invention is referred to as partially depolymerized hyaluronic acid it is extremely unlikely that any polymerized hyaluronic acid remained in it. Although it is speculated that the invention may have acted "as a transport agent, ion-exchanger, or a protective colloid and peptizing agent" (Page 1, lines 28 to 34), its activity in spreading dye in the dermis or facilitating the absorption or activity of saline, X-ray contrast medium or local anaesthetic was comparable to that of hyaluronidase, which was considered to act not as a transport agent itself but by breaking down the impedance provided by the natural meshwork of hyaluronic acid polymers in the skin. Largely because of its inactivation in subsequent usage by acquired immunity, hyaluronidase had been abandoned in clinical use about this time. Despite the purported removal of any immunogenic residue, the invention, PDHA, did not become commonly used in clinical practice (if at all), and it would be most unlikely to provide any motivation for persons skilled in the art to combine its teaching with that of Schultz and Della Valle and thus to render obvious the invention of Falk and Asculai in the representative claims appended as Exhibit 2 hereto. With respect to its use as a carrier of agents through the surface of intact skin, one of the references given by the Examiner (Balazs and Bland in the article "Polymers in Cosmetics. Hyaluronic Acid: Its Structure and Use", Cosmetics & Toiletries, 1984, Vol. 99, pps. 65-72) states *inter alia*,

> " it is not expected that even <u>very short chains</u> (oligosaccharides) <u>of degraded hyaluronic acid</u> that contain more than five to ten disaccharide units can pass <u>through this layer of the skin</u>." (P. 71.

My emphasis. I shall amplify the reasons for this conclusion in a later section.)

On these several grounds, Seifter thus is meaningless with respect to the teachings of the use of hyaluronic acid with medicines, or treatments involving the use of hyaluronic acid and would so be considered by persons skilled in the art. Balazs alone contradicts the assertions of the Examiner with respect to the relevance of Seifter.

Forms of hyaluronic acid have been applied topically to skin, the eye in the conjunctival sac, various mucous membranes and direct to the cavity of synovial joints.

They have been taught to provide "homogeneous, stable" films on the corneal epithelium (Della Valle et al, U.S. Patent 4,736,024). As a corollary to this conclusion, which has since been supported by demonstration of hyaluronic acid binding sites on the corneal surface, there could be no expectation in the prior art that movement of hyaluronic acid itself below the surface of the cornea was responsible for any transport or delivery of medicinal or therapeutic agents within the tissue.

Schultz et al (U.S. Patent 4,808,576) teach that hyaluronic acid applied to sites in the body remote from the joints will be carried to traumatized mammalian joint tissue and relieve the sequelae of this trauma. They emphasize that the hyaluronic acid should have a high average molecular weight, with a single molecular weight peak between 1.2×10^6 and 4×10^6 especially preferred. In describing the application of hyaluronic acid to the skin for this purpose they repeatedly specify that a transdermal carrier is essential to ensure that the hyaluronic acid could pass through the skin. In column 12, lines 14 to 17, they state:

> "The topical application of the sodium hyaluronate without a transdermal carrier was ineffective. The hyaluronate solution simply evaporated to dryness leaving a film on the skin of the subject."

It is a matter of general observation, which I have confirmed for myself, that these dried hyaluronan films tend to break up and visibly flake off the surface if thick enough.

In the invention of Schultz et al., hyaluronan is the medication and when injected into the body finds its way through natural pathways to reach sites where it might influence disease processes just as any drug would do. There is no implication that it is selectively distributed to the site of the disease process, and there is no teaching that it might be used to carry drugs specifically to such sites.

In the case of the film formed by hyaluronic acid on the corneal surface, Della Valle et al showed that it remained stable for more than two hours when formed from a very high concentration (20mg/ml) of medium molecular weight (500,000 to 730,000; column 30, line 21 through column 31, line 9)). The persistence of the film on the cornea is explicable by the moist conditions in the conjunctival sac, together with the elastic-viscose properties of the preparation (column 1, line 47), and adhesion to the corneal epithelium (column 2, lines 48-49). The visco-elastic properties would also be opposed to any deeper penetration of its hyaluronan content. The observations recorded in Della Valle et al and Schultz et al are consistent with what was known at the time in the art. When hyaluronic acid was topically applied to intact surfaces such as skin or cornea it

was not expected to penetrate and did not penetrate according to the teachings in the art prior to 1989.

Hyaluronic acid is a polymer of two small molecules derived from glucose; one by addition of an acetamido group and the other by addition of a carboxylic group. Its primary structure would therefore indicate strongly hydrophilic properties, which it certainly exhibits. It is well established that purely hydrophilic substances penetrate the keratinised outer layer of the skin very poorly, whereas lipophilic or amphiphilic substances do so much more readily. Accordingly, neither hyaluronic acid nor oligosaccharides derived from it would have been expected to penetrate the skin by persons skilled in the art who were aware of these facts. The views of persons skilled in the art at that time were succinctly expressed by Balazs and Bland in the article of 1984 quoted earlier, as follows. (It should be noted that Balazs is held in the highest esteem by people working in either field for his contributions to both the basic science and the therapeutic applications of hyaluronan.)

> "The stratum corneum is known to be impermeable to molecules as large as hyaluronic acid; therefore, it is not expected that even very short chains (oligosaccharides) of degraded hyaluronic acid that contain more than five to ten disaccharide units can pass through this layer of the skin. There is no evidence in the literature that any hyaluronic acid - in any solvent or with any carrier - will penetrate any deeper than the crevices between the desquamating cells."

(The desquamating cells are those dead cells being constantly shed from the skin.)

(a) U.S. Patent 3,887,703 teaches the use of purified mucopolysaccharides (which include hyaluronan) in cosmetic and pharmaceutical preparations, used in various combinations with other ingredients for application to the skin, injection or ingestion by mouth. The relative content of hyaluronan and other

glycosaminoglycans (mucopolysaccharides) is not stated, and the molecular weight of the mucopolysaccharides ranges between 5,000 and 2,500,000. The cosmetic preparations were used by applying several drops for reduction of greasiness of scalp and hair (columns 20 to 22). All of them contained alcohols or other substances capable of dissolving or dispersing oily and fatty materials and in some examples (e.g., examples 13, 14, 15, 17) allantoin and in example 14, also salicylic acid, which is used to soften and dissolve keratin on the skin. No suggestion was made that the mucopolysaccharides might penetrate the skin in these examples, and others skilled in the art would not find it necessary to postulate such a result to explain the effects. Application of the mucopolysaccharide preparation to the skin was also shown (i) to reduce the greasiness of hair and superficial fat content of skin induced in biotin-deficient rats and (ii) to reduce the fat and water content of ovariectomised rats. These results can be explained without invoking penetration of the skin by the mucopolysaccharides. Topical application was also shown to reduce the time for cicatrization (that is, scarring) of the skin after irradiation with ultraviolet light. The occurrence of scarring indicates that the reaction to UV would have caused blisters and ulceration, which would greatly increase the permeability of the skin. The same preparations were also used by intraperitoneal or intramuscular injection to reduce inflammation of various kinds. Apart from the case of UV burns, the only example of topical application to relieve inflammation (column 12, lines 21 to 32) is not presented with sufficient data for critical evaluation. It must be noted that in contrast with hyaluronan every disaccharide unit of the other glycosaminoglycans in this mucopolysaccharide preparation contains at least one additional negatively charged group (sulfate) which could further reduce their capacity to penetrate the hydrophobic barrier in skin. On the other hand the molecular weight of sulfated glycosaminoglycans is always relatively low, being mostly in the order of 30,000 or less and therefore much less than most examples of hyaluronic acid. The greatest difficulty in comparing the

teaching of this patent with those of Falk and Asculai arises, however, from the unknown and probably variable proportions of several glycosaminoglycans in the preparations, and the much greater variation in their molecular weight. The examples and other information contained in this patent would not render the teachings of Falk and Asculai obvious to persons skilled in the art. U.S. Patent 3,887,703 was issued June 3, 1975.

(b) U.S. Patent 4,141,973, which issued February 27, 1979 teaches high molecular weight forms of hyaluronic acid (molecular weight preferably exceeding 1,200,000 daltons). At column 14, lines 30-37, Balazs indicates that the high molecular weight form of hyaluronan can be used as a vehicle for any kind of intra-articular medication to protect the articular cartilage from the possible harmful effects of the particular drug used and to prolong the effect of the drug by decreasing its diffusion out of the articular space. To me and to persons skilled in the art this teaching means that the combination of the form of hyaluronan having the high molecular weight, together with the drug, for example, corticosteroid, is injected into the intra-articular space and because of the high molecular weight of the hyaluronic acid the effect of the drug is prolonged by decreasing (delaying) its diffusion out of the articular space providing a retard effect. This retard effect, to reiterate, is provided by the way of a viscous high concentration of hyaluronic acid of high molecular weight, which leaves the articular cavity more slowly, so that the medication (for example, corticosteroid) can leach therefrom and be absorbed by the inflamed tissues for a longer period.

(c) The foregoing statements are in my opinion a precise account of what was known to persons skilled in the art. Persons skilled in the art did not expect, prior to 1989, that hyaluronic acid would penetrate the skin. I cannot agree with the conclusion that the use of dermatological preparations suggested in Della Valle's patent (U.S. Patent 4,736,024) would provide ample motivation for one of

ordinary skill in the art to achieve a therapeutic response in the skin even by altering their content of hyaluronic acid. Without the knowledge that hyaluronic acid could penetrate deeper than the desquamating cells being shed from the skin, it would be expected that in contrast with its application to the obviously different corneal environment in the eye, it would simply dry up and flake off the skin. No evidence was presented to suggest that adherent and stable films would be formed on application to mucous membranes such as the mouth, and it must be noted that the preparations would be diluted and washed away from the intended site of action by the secretions generated by such membranes or delivered to the area by associated glands; for example, saliva in the mouth. Della Valle et al also suggest the use of suppositories containing hyaluronan to obtain a systemic effect. To permit effective rectal insertion, suppositories must be virtually solid at room temperature. Even the highest concentrations of hydrated hyaluronic acid would be too soft. In any case, the mucous membrane of the rectum does not present a barrier to drug absorption comparable to that of the skin.

(d) The background to the invention described in U.S. Patent 4,736,024 makes the completely acceptable statement that application of a topically active medicament may be of benefit, especially in diseases of the outer eye, skin and other body surfaces. The special advantages of the invention are asserted that hyaluronic acid creates a more efficient vehicle for drugs and provides better bioavailability (column 1, lines 35-38).

The essence of the invention in therapeutic terms is summarized in column 2, lines 44 to 51, as follows. "The use of hyaluronic acid as a vehicle for ophthalmic drugs allows for the formulation of excellent preparations free from concentration gradients of the active substance and, therefore, perfectly homogenous, transparent and adhesive to the corneal epithelium, without

sensitization effects, with excellent vehicling of the active substance and possibly retard effects." (My emphasis.) It is then stated in the following sentence that the properties just specified may also be used in diseases of the skin or mouth, and to obtain a systemic effect from transcutaneous reabsorption, for instance from suppositories. This claim rests critically on the ability of the invention to form an adhesive film on the cornea which is stable for some hours, and permits the medication not to be rapidly washed away by tears (into the nose - supporting evidence for this is given in columns 30 & 31).

(e) It is therefore clear that persons skilled in the art would expect such a film to form only in the special conditions of the cornea. Since it is made clear that the major advantages of the invention rest on the formation of this film and the available information at that time made it extremely unlikely that a similar persistent stable film would form on the skin or other surfaces, Della Valle et al would not have provided motivation at that time to prepare dermatological preparations even with modified compositions or dosages because of the reasons given earlier in this declaration. Persons skilled in the art would not have expected hyaluronic acid to penetrate the skin sufficiently to escape drying and flaking from the surface. I would myself have reached such conclusions and must respectfully disagree with the conclusion that Della Valle et al had made the invention of the applicant obvious to persons skilled in the art.

(f) Furthermore, there is nothing in Della Valle to teach the administration intravenously, intramuscularly or intrapleurally or by any other route into the body except by topical application. In said Della Valle patent, dosage amounts of drops of combinations of hyaluronan (less than 1mg) and antibiotics are inserted into an animal's eye where, because of the compatibility of hyaluronan with the eye and because of the viscosity of the hyaluronan in the eye the antibiotic is retained in contact with the surface of the eye where the hyaluronan purportedly

provides a retard effect for the antibiotic. Thus, it acts not as a carrier of drugs within the tissue surface, but as a reservoir of drug on the surface.

(g) U.S. Patent 4,711,780, issued December 8, 1987 discusses the use of hyaluronic acid in formulations in reproductive tract treatments using mucopolysaccharides. Two of the mucopolysaccharides are chondroitin sulfate and hyaluronic acid which are preferred for the treatments in the reproductive tract. Mucopolysaccharide, according to the inventors, act as a <u>barrier</u>, thereby preventing toxins (*sic*) on the skin surface from penetrating into the blood circulation, which otherwise leads to septicemia (see column 5, lines 25-28). (It must be noted here that toxins can be the product of bacterial infection but do not develop into bacterial infection such as septicemia.). A number of formulations are provided (see example 4, 5, and 6) dealing with the reproductive tract which may contain, according to the teachings of the patent, hyaluronic acid. However, the hyaluronic acid is stated to act as a barrier. In this regard high molecular weight hyaluronic acid is well known to act as an impedance or bar to the passage of both molecular and particulate matter. No teachings or usage or methods are taught which show the use of hyaluronic acid for transportation purposes in this invention.

(h) While I have endeavoured to discuss U.S. Patent 4,736,024 briefly above, and repeat the statements made previously, it is also my opinion that the teachings of the said U.S. Patent 4,736,024 do not teach methods of treatment using dosages containing minimum amounts of at least 10 mg of the form of hyaluronic acid together with an effective amount of a medicine or therapeutic agent. The said patent teaches the use of drops or solid (dry) preparations containing combinations of hyaluronan and a medicinal or therapeutic agent in which dosage amounts of much less than 1 mg are applied to the eye. In the unique conditions prevailing in the conjunctival sac at the front of the eye, it

shows that these combinations form a uniform, stable film adherent to the underlying tissue, "possibly with a retard effect" (column 2, line 51). For the reasons presented in sections (d) to (f) above, persons skilled in the art would not have expected similar consequences to follow the application of such a combination to the skin or mucous membranes as claimed in column 2, lines 52-64, regardless of any variation in the amount of hyaluronic acid, or the proportions of hyaluronic acid and medicament. In regard to transcutaneous absorption (or more strictly speaking, transmucosal in the case of suppositories), Della Valle et al do not teach transport of the medicament across the skin or mucous membrane but refer only to absorption. To be effective this would require a stable film to be retained at the surface of the skin or mucous membrane for a sufficient time to allow absorption, which as indicated above would not be expected from the knowledge available at that time. It is still true that for agents to penetrate skin effectively, they should be at least partly lipophilic. As explained above, in 1989 a person skilled in the art would have believed hyaluronic acid to be strongly and solely hydrophilic, as I did myself at that time.

Furthermore, there is no teaching in Della Valle et al., either direct or implied, that intravenous, intramuscular or other injectable routes can be used to deliver formulations of hyaluronic acid and drugs or medications for the treatment of disease.

Even to this date, the use of hyaluronan in the eye in small drops has been tested by Dr. Ian Constable and the result published in Round Table Series #40, 1995. In this article, a copy of which is attached as Exhibit 3 to this my declaration, Professor Constable discusses the administration of drops of hyaluronan and NSAIDS in the eye. He clearly states at page 141:

"It does not get to the back of the eye. Available data on combining HA with drugs in drops show rapid clearance from the anterior chamber. Dr. Gustafson has published data on receptors in the corneal epithelium, and nothing gets to the back of the eye if administered as drops."

These observations were made as late as 1995.

(i) I have also been given a copy of an article entitled "Effect of Several Penetration Enhancers on the Percutaneous Absorption of Indomethacin in Hairless Rats", Chem. Pharm. Bull. 36(4), 1519-1528(1988). In that article there is a discussion of the effect of several penetration enhancers on the percutaneous absorption of drugs. Note the use of the expression "percutaneous absorption". In other words the medicine is absorbed through the skin and the penetration enhancers enable such absorption. One of the compounds tested was sodium hyaluronate, but the investigators found that it did not enhance permeation of indomethacin through the skin. The molecular weight of the hyaluronate was not stated. If it should be very high, I would not expect it to penetrate the skin even allowing for its amphiphilic character. The experiments were also done in excised skin placed in a diffusion chamber up to 32 hours, exposed on the outer surface to the medicaments, and on the undersurface to a buffered salt solution which contained no glucose, potassium or other essentials to maintain full cellular function or viability.

Thus, all the articles that I have referred to, even when read together, provide no motivation for making either topically applied dosage amounts of formulations or intravenous, subcutaneous, injectible or the like dosage amounts of formulations which are administered onto/into the body by the use of minimum amounts of 10mg of hyaluronic acid having a molecular weight

less than 750,000 daltons together with an effective dosage amount of a therapeutic agent because the prior researchers did not appreciate that hyaluronan could transport the medicine and such persons did not appreciate that such formulations, for example those of Della Valle with respect to dermatological formulations, could be effective. There was no motivation to produce such formulations.

5. I have carefully reviewed the teachings in the PCT application which entered the National Phase in the United States Patent Office as I am advised by Ivor Hughes, Patent Agent, under Application Serial Number 07/675,908 and the claims attached as Exhibit 2 to this my declaration. The claims are of two types. The first type is, I understand, representative of dosage amounts of compositions containing minimum amounts of forms of hyaluronan of 10mg having a maximum specified molecular weight together with an effective amount of a therapeutic agent. The second type of claim is representative of method claims using the dosages in the treatment of underperfused tissue and/or pathological tissue. It is not that the therapeutic agent is new; rather it is the dosages which are new that provide enhanced transport of the agent to the site in need of treatment.

6. It is not every disease or condition for which, on my understanding of the application, the invention can be used. As described at page 24, beginning at line 13, the combination of the hyaluronic acid in the appropriate dosage amounts (greater than 10mg when administered), together with the drugs or other therapeutic agents produces an unusual targeting for underperfused tissue and/or pathological tissue. This is the specific area to which the invention relates. In other words, where the treatment involves underperfused tissue and/or pathological tissue, the form of hyaluronan targets the underperfused tissue and/or pathological tissue with the drug/therapeutic agent/medicine

which is used to treat the underperfused tissue and/or pathological tissue. The application then lists throughout its disclosure a substantial number of conditions and diseases which can be treated by the invention and which involve, according to the teachings of the patent, underperfused tissue and/or pathological tissue. Representativesof the conditions and diseases which involve underperfused tissue and/or pathological tissue are specified in Claim 61. These listed conditions and diseases are not inclusive of all conditions and diseases involving underperfused tissue and/or pathological tissue. They are, however, representative according to the teachings of the application. They are all found in the application.

7. As I understand the expression underperfused tissue and as is confirmed by the teachings in the application at page 24, underperfused tissue involves tissue, such as a kidney, which is underperfused or malfunctioning due to insufficient blood flow (see page 24, lines 31-33). The tissue being underperfused is therefore underperfused with respect to blood.

8. Pathological tissue includes underperfused tissue. Pathological tissue involves tissue which pertains to or results from the effects of a disease or condition which destroys the tissue or changes it from its normal condition. Underperfused tissue will inevitably be hypoxic which can result in necrosis of the tissue or extreme pathological change. Many pathological changes, if not reversed, can cause necrosis of tissue. Even transient underperfusion, followed by reperfusion, will lead to pathological changes.

When tissue is underperfused and hypoxic, a point is eventually reached when the capillaries become more permeable. This pathological change to the tissue would additionally then facilitate the delivery of the form of hyaluronan associated with the drug into the affected tissues (aside from the effect of

hyaluronan in the dosages). Thus, as tumors need blood vessels and capillaries for the transportation of blood into the tumor and because the blood vessels and capillaries to the tumours are defective there is increased permeation of blood plasma and often frank bleeding in the tumour and these blood vessels, because of their permeability enable delivery of the form of hyaluronan and the medicine.

9. Since the writing of the application, much has been learned with respect to the causes of the unusual alteration of the drugs' distribution and performance in the human body and the production of the unusual targeting for underperfused tissue and/or pathological tissue. Today, we know that such tissue generally expresses excess hyaluronan receptors which causes the form of hyaluronan administered to target such underperfused and/or pathological tissue. This is discussed in a number of articles that have now been published and may even be discussed in a number of later patent applications. Two of such articles were published in the Second International Workshop on hyaluronan drug delivery and the Third International Workshop on hyaluronan and drug delivery which were published in or about 1995 and thereafter. One article is entitled "Targeting of Hyaluronan to Tumours Via Binding to ICAM-1" (ICAM-1 is not, we have now discovered, a hyaluronan receptor; however, there are other receptors such as RHAMM and CD-44). Another such article is entitled "Role of Hyaluronan Receptors in Breast Carcinoma". I attach copies of the articles as Exhibit 4A and 4B to this my declaration. The point is that this patent application teaches that the combination is now targeting to the pathological tissue, even when administered by the systemic intravenous route (page 25, lines 29-31).

10. Additionally, when the amount of hyaluronan exceeds 200mg in the dosage, the toxic side effects which usually occur with NSAIDS, such as gastro-intestinal distress, neurological abnormalities, depression, etc., even at elevated

amounts of the NSAID, indomethacin, are reduced. As each patient would be affected differently the reduction of the side effects would vary. Some persons would have the side effects eliminated and others the side effects only reduced. The point is, however, that it is the combination of the hyaluronic acid at the minimum amount of 200mg and the drug which causes the reduction of the side effects.

It is thus the minimum amount of 10mg of the hyaluronic acid which enhances the transportation and delivery to the underperfused and/or pathological tissue. The differentiation between all tissue and underperfused and/or pathological tissue is not made in the prior art. There is not even any discussion. Therefore, no undue experimentation to determine the diseases and conditions generally need be ascertained. If underperfused tissue and/or pathological tissue is involved, then persons skilled in the art will understand that this invention applies to such tissue and can be used with such tissue in the treatment thereof. The claims in Exhibit 2 as now presented reflect my comments above and, in my opinion, the subject matter thereof is clearly and unequivocally taught in the application. The conditions and diseases listed are all specified in the application. More broadly, the pathological tissue and/or underperfused tissue to which they all relate is also described. The dosage amounts all relate to medicinal agents and therapeutic agents in therapeutically effective amounts to treat the disease or condition involving underperfused tissue and/or pathological tissue.

11. These dosages, but for Applicants' invention, for treatment would not have been developed by persons skilled in the art because there was no reason to develop such dosages. For example, the fact persons skilled in the art would not use Della Valle's teachings to provide dermatological dosages because persons skilled in the art would expect the form of hyaluronan to dry and flake off. This

drying and flaking off would have directed persons skilled in the art in other directions from developing Applicants' formulations. United States Patent 4,808,576 is to the same effect. In fact, in Schultz, hyaluronan is the medicine.

It is thus clear that Applicants' dosages are not taught by the prior art.

Thus, with respect to paragraphs 6, 7, 8 and 10 of my declaration referencing particular disorders to be treated, the application does not relate to any arbitrary disorder or condition. Cancers generally involve pathological tissue and having regard to the number of different cancers treated successfully in the application, Applicants have clearly taught that the invention can be applied to all cancers because they involve pathological tissue. The different cancers described in the application are:

[redacted]	[redacted]
Laryngeal Epidermoid	Case I, page 36
Malignant Melanoma	Case II, pages 36-37
Cancer of the Gallbladder	Case III, page 38
Cancer of the Colon Metastatic to the Liver	Case IV, pages 38-39
Transitional Cell Cancer of the Bladder	Case V, pages 39-40
Right Upper Lobe Lesion	Case VI, pages 40-42
Cancer of the Breast	Case VII, pages 42-45 Case XI, pages 47-48 Case XIV, pages 50-51
Tumour in the Right Upper Lobe of the Lung	Case VIII, pages 45-46
Gastric Cancer	Case IV, pages 46-47
Hepatoma	Case X, page 47
Leomyosarcoma of the Uterus	Case XIA, page 48
Inguinal Recurrent Melanoma	Case XIB, pages 48-49
Stomach Cancer	Case XVII, page 52
Colon Cancer	Case XVIII, pages 52-53 Case XX, page 54
Carcinoma of the Lung	Case XIX, pages 53-54
Cancer of the Uterus	Case XXI, page 54
Adenocarcinoma	Case XXII, pages 54-55
Intraperitoneal Tumor	Case XXIII, pages 55-56

Carcinoma of the Pancreas	Case XXIV, page 56 Case XXV, page 56
Carcinoma of the Ovary	Case XXVIII, pages 57-58
Epitheloid Sarcoma	Case XXXI, pages 58-59
Gastric Cancer	Case XXXII, pages 60-61
Carcinoma of the Cervix	Case XXXVII, pages 64-65

With respect to the side effects of drugs, the application discusses and exemplifies the reduction of side effects of an NSAID at pages 25 and 26 (and in the cases). However, the comments are equally applicable to other drugs where they do have side effects because, first of all, drugs which are now being targeted to a site in need of treatment would be directed from other areas where the side effects are generated. For example, side-effects of the drug arising from action on the nervous system would be reduced, since the blood capillaries of the brain are amongst the least permeable in the body and association of a drug with the very large molecules of hyaluronan would greatly reduce its passage into the brain substance. Association of the drug with hyaluronan would also reduce its dissemination to other sites where side-effects are generated (such as the stomach), since any hyaluronan not delivered to the pathological tissue is predominantly removed from the blood by the liver and to a lesser extent by the kidneys (approximately 80-90% and 10% respectively). These organs are major sites for the inactivation or excretion of many drugs. Promotion of elimination of the drug by these routes is also an advantage in reducing dosage excess, which cannot always be predicted with certainty due to the inherent variation in individual sensitivity.

Finally, with respect to AIDS, the Applicants have exhibited an example involving AIDS - AIDS involves pathological tissue. Further, the body suffers from other diseases arising from impairment of the immune system by the HIV virus. Thus, persons suffering from AIDS suffer from other diseases and Example 40 discusses a patient diagnosed with AIDS who had an undetermined

neoplastic disorder in the lungs. When a patient has fully developed AIDS, the patient has underperfused and/or pathological tissue which will be capable of being treated using Applicants' invention.

12. With respect to the expression "dosage amount", the claims do not now include a reference to a 70kg person. However, the reference to a 70kg person remains in the application and as I understand the application, the 70kg person is a representative person to whom the proposed dosages will be delivered. Persons skilled in the art reading the application will adjust the dosage amount to the person being treated.

13. With respect to a dosage excess, I can understand the Examiner's point with respect to the intended result of administration. Component (1) (the agent) would be required to be known in order to determine whether or not the dose of the medicine is a dosage excess. However, when dealing with the treatment of diseases and conditions, persons skilled in the art will realize a dosage excess means an amount greater than normally used for that condition or disease.

14. Having previously discussed the state of the art and the teachings of the application, it should now be clear that the claims are [redacted] free of the prior art previously commented upon. The Examiner has rejected the claims to dosages under 35 U.S.C. §103 as being obvious over Della Valle and the same claims and the method claims as being obvious over Seifter in view of Schultz and Della Valle as evidenced by the Balazs article.

In my opinion, the dosage claims that are presently before me and attached to my declaration as Exhibit 2 are not obvious over the Della Valle reference because there is no motivation to make the dosages. Persons skilled in the art would believe that the dosages would not be useful - persons skilled in the art

would believe in 1989 that they would not be effective except for drops in the special conditions in the cornea. Applicants' claimed dosages would not, therefore, exist but for the fact of Applicants' unique methods of treatment because there would be no other reason to make them. Thus, with respect to the rejection of the method and dosage claims based on Selfter, Schultz, Della Valle and Balazs, Selfter does not relate to hyaluronic acid as is clear from my earlier statements in my Declaration, Schultz is not suitable for topical use of hyaluronic acid by itself and Della Valle does not provide any motivation to make the dosages or carry out the methods. In fact, the Balazs article states that topically there is no evidence in the literature that any hyaluronic acid in any solvent, or with any added carrier, will penetrate deeper than the crevices between the desquamating cells. This was in 1984. The position had not changed by 1988 by the issuance of Schultz (U.S. Patent 4,808,576) or by the issuance of Della Valle (U.S. Patent 4,736,024) when persons skilled in the art would not have expected the dermatological preparations to penetrate the skin or even to adhere to it as they did in the eye. I cannot agree with the conclusions reached by the Examiner. There is no motivation in Della Valle, taken alone or together with the other patents cited, that could lead anyone to develop the methods of treatment as taught by Applicants, nor is there any motivation to teach the dermatological preparations that are used in the methods of treatment. Applicants' dermatological preparations are therefore not obvious. The dermatological preparations did not exist. Furthermore, the combination of the form of hyaluronic acid (having a minimum amount of 10mg) together with an agent which is suitable for use to treat underperfused and/or pathological tissue is not taught. There is no teaching of Applicants' methods and Applicants' dosage preparations including dermatological preparations in the prior art. There is no teaching of the treatment of underperfused and/or pathological tissue.

15. In view of the unique dosage combination containing an amount of at least 10mg of a form of hyaluronic acid having a molecular weight less than 750,000 daltons and an effective amount of the medicinal and/or therapeutic agent, which combination is used to treat underperfused tissue and/or pathological tissue, the unexpected properties of the dosages and the unexpected treatment resulting from using the dosages provides unexpected benefits to the patient. In my opinion, the subject matter of each and every one of the claims attached as Exhibit 2 to my declaration with the limitations in the claims constitutes a new invention over and above the prior art. There is no teaching of the dosages and treatments in the prior art nor any motivation in the prior art to make these dosages for any treatments. Nowhere is there any teaching of these dosages or the unexpected benefits provided by those dosages. In my opinion, the invention provides unique and totally unexpected benefits over the prior art.

16. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements will jeopardize the validity of the application and any patent issuing thereon.

EXECUTED this 20th day

of June, 1997

JOSEPH ROBERT EMMOTT FRASER